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10/565,741	01/23/2006	Yolande Chvatchko	ARS120	2192

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,741	CHVATCHKO, YOLANDE	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-39,41 and 45-56* is/are pending in the application.

4a) Of the above claim(s) *27 and 49-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-26, 28-39, 41 and 45-48* _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 03/18/08, is acknowledged.

2. Claims 24-39, 41 and 45-56 are pending.

Newly added claims 49-56 are directed to non-elected invention because the newly added mechanism of action "recruitment of lymphocytes, macrophage and neutrophils in an individual", is neither part of the elected invention nor contemplated in the specification to treat MS.

3. Claims 27 and 49-56 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 24-26, 28-39, 41 and 45-48 are under consideration in the instant application they read on a method of treating inflammatory and/or autoimmune diseases comprising the administration of a composition comprising a soluble protein comprising a sequence having at least 85% of homology with the mature form of the extracellular domain of human CD164 (SEQ ID NO: 1) and SEQ ID NO: 1 and multiple sclerosis as the species.

5. Applicant is advised that should claim 24/45 be found allowable, claim 26/47 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

6. Applicant's IDS, 3/18/08, is acknowledged.

7. The following new reject is necessitated by the amendment filed 3/18/08.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 45-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 45 is ambiguous because it is not clear how the soluble CD164 which has the property of inhibiting the cellular expression of cytokines IFN-γ, IL-2, IL-4, IL-5 and IL-10, would only inhibit ALAT, IFN-γ or IL-6 level *in vivo*.

10. In view of the amendment filed on 3/18/08, only the following rejections are remained.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 24-26, 28-39, 41 and 45-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of inhibiting the proliferation of MBP specific T cells induced by AC1-11 comprising contacting said cells with soluble CD164 polypeptide, does not reasonably provide enablement for a method of treating Multiple sclerosis comprising the administration of a composition comprising a soluble protein having at least "95% of identity to the mature form of the extracellular domain of human CD164 (SEQ ID NO:1)", said soluble protein inhibiting the cellular expression of cytokines selected from interferon-γ, TNF-α, IL-2, IL-4, IL-5 and IL-10 in claim 24, or a method of inhibiting the expression of one or more cytokines in an individual comprising administering to said individual a composition comprising a soluble protein comprising a sequence having "at least 85% of homology with the mature form of the extracellular domain of human CD 164 (SEQ ID NO: 1)" and wherein said cytokine is interferon-γ, TNF-α, IL-2, IL-4, IL-5 and IL-10; or a method of reducing alanine transanimase (ALAT), IFN-γ, or IL-6 levels in an individual comprising the administration of a composition comprising a soluble protein having at "least 95% identity" to the mature form of the extracellular domain of human CD 164 (SEQ ID NO: 1), to an individual in an amount sufficient to reduce said levels of ALAT, IFN-γ or IL-6, said soluble protein inhibiting the cellular expression of cytokines selected from interferon-γ, TNF-α, IL-2, IL-4, IL-5 and IL-10 in claim 44. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record.

Applicant's arguments, filed 3/18/08, have been fully considered, but have not been found convincing.

Applicant submits that the Office Action argues that the as-filed specification fails to enable the claimed methods of treatment (in vivo) and provides a number references supporting its arguments that animal models are not considered predictive of the results obtained in humans with respect to the treatment of multiple sclerosis. Applicant respectfully asserts that there is adequate written description in the subject specification to convey possession of the claimed invention to the skilled artisan and that the claims are enabled by the subject specification.

However, it remains the Examiner's position that the specification does not adequately teach how to effectively treat any inflammatory and/or autoimmune diseases including MS or reach any therapeutic endpoint in humans by administering the sCD164. The specification does not teach how to extrapolate data obtained from in cell-based assays to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention.

Applicant submits that a focus on the clinical failure of therapeutic compounds for treating multiple sclerosis that were identified via the EAE animal model is an insufficient basis for rejecting the claims of this matter where they are directed to methods of treating multiple sclerosis (MS). As noted by Baker and Jackson, MS appears to be a uniquely human condition and no other animal spontaneously develops a disease identical to MS. Further, the authors indicate that while EAE may be an imperfect model, it has been used to shape therapeutic approaches for the treatment of MS for decades and the failure to detect viable treatments may be the result of how studies are interpreted by the scientific and medical community (see page 10, column 2, last paragraph). Baker and Jackson also indicate that EAE is a leading research tool for the identification of MS therapies (see page 11) and that while a number of agents shown to ameliorate EAE have failed in the clinic, the development of drugs such as Tysbari have been critically dependent upon such animal models (page 11, column 3, last paragraph). Additionally, Steinman and Zamvil (Ann. Neurol., 2006 60:12-21) discuss how one can successfully apply EAE models to MS. Indeed, the reference indicates that EAE has lead to the development of three therapies for MS and several new approaches for the treatment of MS are in clinical trials based upon positive results obtained in the EAE model (see Abstract). Steinman and Zamvil also discuss problems and promise surrounding the use of EAE models for the development of therapies for MS (see pages 16-19). Here, it is indicated that there is a long list of drugs that have shown promise in EAE models that are now being taken forward into the clinic. Other approaches, such as sphingosine inhibitors, statins, carboxamido and an IL-2 monoclonal antibody have shown promise in phase 2 trials and were first based upon success in the EAE model (page 16, colmml 1, paragraph 1). Thus, it is respectfully submitted EAE models are art recognized acceptable models for the identification of candidate compounds for the treatment of MS.

While the Examiner agrees with Applicant that the EAE models are art recognized acceptable models for the identification of candidate compounds for the treatment of MS, however, no such EAE model is used in the instant specification to demonstrate that the sCD164 is a candidate compound for the treatment of MS.

Regarding the lack of teaching with respect to the relationship of the MBP specific T-cells activated by the Acl-11 peptide, Applicant points to Example 5 indicates that the claimed polypeptide is able to inhibit the proliferation of MBP specific T-cell clones, cells recognized to be a target for MS therapies. Thus, Applicant respectfully submits that the ability of the claimed polypeptide to inhibit proliferation of MBP specific T-cells would have indicated that the claimed polypeptide was a candidate compound suitable for the treatment of MS and those skilled in the art would have known how to use such a candidate compound in view of the state of the art at the time the invention was made.

However, while sCD164 inhibition of proliferation of MBP specific T-cell clones and induces the production of T-helper 2 cytokines, however, it is unpredictable whether it would contribute to therapeutic benefit in MS. In the absence of an animal model to test sCD164, this observation only serve as the basis for further research on the observation itself. While the specification identifies sCD164 as a compound that *might* work, this description, without more precise

guidelines amount to little more than, "a starting point, a direction for further research." *Genentec, Inc. V. Novo Nordisk* A/S, 108 F.3d 1361, 1366, 42 U.S. PQ.2d (BNA) 1001, 1005 (Fed. Cir. 1997). The influence of a scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic. Yet such empirical and demonstrable aspects of the claimed method of treating MS with the sf-CD164 are lacked in the instant specification. No working empirical data demonstrating that the sf-CD164 would treat or reduce the severity of MS is disclosed. The specification does not teach how to extrapolate data obtained from in a cell-based assay from MBP-specific antigen processing and presentation to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the sf-CD164 exemplified in the specification.

With respect to the issues raised with regarding claims 41 and 42, Applicant respectfully submits that the Office Action improperly rejects these claims as related to the treatment of MS. Applicant submits that the claims are directed to methods of reducing the production TNF-α, IL-2, IFN-γ,, IL-6, IL-5 and IL-10. The as-filed specification clearly indicates that the claimed polypeptide is capable of reducing the expression of these cytokines by cells (see Example 2 and Example 6). Accordingly, it is respectfully submitted that this aspect of the invention is enabled and reconsideration of this rejection is respectfully requested.

However, it appears that Applicant argues that the mechanism of action of sCD164 on MS does not involve TNF-α. However, the claimed sCD164 would be inhibited the expression of the TNF-α *in vivo* as claimed.

13. Claims 24-26, 28-39, 41 and 45-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

Applicant is in possession of an in vitro method of inhibiting the proliferation of MBP specific T cells induced by AC1-11 comprising contacting said cells with soluble CD164 polypeptide.

Applicant is not in possession of a method of treating Multiple sclerosis comprising the administration of a composition comprising a soluble protein having at least "95% of identity to the mature form of the extracellular domain of human CD164 (SEQ ID NO:1)", said soluble protein inhibiting the cellular expression of cytokines selected from interferon-γ, TNF-α, IL-2, IL-4, IL-5 and IL-10 in claim 24, or a method of inhibiting the expression of one or more cytokines in an individual comprising administering to said individual a composition comprising a soluble protein comprising a sequence having "at least 85% of homology with the mature form of the extracellular domain of human CD 164 (SEQ ID NO: 1)" and wherein said cytokine is interferon-γ, TNF-α, IL-2, IL-4, IL-5 and IL-10; or a method of reducing alanine transanimase

(ALAT), IFN-γ, or IL-6 levels in an individual comprising the administration of a composition comprising a soluble protein having at "least 95% identity" to the mature form of the extracellular domain of human CD 164 (SEQ ID NO: 1), to an individual in an amount sufficient to reduce said levels of ALAT, IFN-γ or IL-6, said soluble protein inhibiting the cellular expression of cytokines selected from interferon-γ,, TNF-α, IL-2, IL-4, IL-5 and IL-10 in claim 44.

Applicant's arguments, filed 3/18/08, have been fully considered, but have not been found convincing.

Applicant submits that the as-filed specification provides adequate description of the claimed invention such that one skilled in the art would have recognized that Applicant was in possession of the claimed invention, particularly in view of the claim amendments presumed herewith regarding the treatment of multiple sclerosis. With respect to the written description issue raised regarding polypeptides having a specified percentage of identity to SEQ ID NO: 1, Applicant respectfully submits that various isoforms of the CD 164 polypeptide were known at the time the application was filed as were functional domains and motifs of the CD164 polypeptide (see paragraph bridging pages 5-6 and Chan et al. (Ref. R9 of the IDS submitted August 28, 2006 at pages 2142-2143 and 2146-2147)). As the Patent Office is aware, the written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.., i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. See Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Additionally, the courts have noted that there is no "per se rule that the information must be information related to a given biological molecule is available in the prior art. See Capon v. Eshhar, 76 USPQ2d 1078, 1084-1085 (Fed. Cir. 2005). Thus, it is respectfully submitted that the written description requirement of section 112 is met by the combined physical and functional characteristics of the soluble protein recited in the claims coupled with the knowledge in the art with respect to the CD164 polypeptide. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner directs Applicant's attention to the new Written Description guidelines (2008), specifically, Examples 10 and 11. In the instant case the specification discloses the reduction to practice of one species within the claimed genus, specifically, the protein having the amino acid of SEQ ID NO: 1. There are no drawings or structural formulas disclosed of any other proteins that inhibit the cellular expression of cytokines. The recitation of a polypeptide with at least 95% identity, 85% homology to extracellular form of SEQ ID NO: 1 represents a partial structure. That is the claimed proteins share at least 95% or 85% of the structure of SEQ ID NO: 1, while up to 5% or 15% of the structure can be varied while retaining the ability of the protein to inhibit the cellular expression of cytokines. Furtehr there is no art-recognized correlation between any structure (other than SEQ ID NO: 1) and the activity of inhibiting the cellular expression of cytokines, based on which those of ordinary skill in the art could predict which amino acids can vary from SEQ ID NO: 3 without losing the catalytic activity. Consequently,

there is no information about which amino acids can vary from SEQ ID NO: 1 in the claimed genus of proteins and still retain the inhibition of cellular expression of cytokines.

There is tremendous variability in the importance of individual amino acids in protein sequences. Since the *O*-linked glycans of CD164 is a key determinant its cytokine activity, residue substitutions can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. CD164 has the common characteristic of being highly glycosylated polypeptides, containing both O- and N-linked carbohydrate side chains. Monoclonal antibodies against CD164 that alter the adhesive and proliferative properties of hematopoietic precursors recognize epitopes that are destroyed by treatment of cells with sialidase, which cleaves terminal sialic acid residues on O- or N-linked carbohydrates, or *O*-sialoglycoprotease, an enzyme that selectively degrades *O*-sialomucins (see Lee et al IDS ref.). It would be predicted, therefore, that amino acid substitutions in the soluble CD164 molecule would effect CD164 cytokine activity. Importantly, ZANNETTINO (IDS *ref.)* teaches that the function of CD164 is not known. Zannettino et al (IDS ref) teach that murine MGC-24v and rat endolyn share significant sequence similarities with human CD164. However, CD164 lacks the consensus glycosaminoglycan (GAG)-attachment site found in MGC-24 (see page 2625, 1st col., top ¶). The specification fails to provide guidance on the importance of the GAG motif modification in the treatment of inflammation/autoimmune diseases.

Although the disclosure of SEQ ID NO: 1 combined with the knowledge in the art, would put one in possession of proteins that are at least 95% or 85% identity/homology to SEQ ID NO: 1, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those proteins having at least 95%/85% identity/homology to SEQ ID NO: 1 (if any) have the activity of inhibiting the cellular expression of cytokines. Basked on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that the applicant was in possession of the claimed genus of proteins based on disclosure of the single species of SEQ ID NO: 1. See Ex parte Kubin (B.P.A.I. 2007).

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 5, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644